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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,121	05/16/2003	Karin Klokkers	4271-34PUS	8059

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EXAMINER	
GHALI, ISIS A D	
ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,121	KLOKKERS ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,10-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,10-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' response filed 08/10/2010 to the non-final office action mailed 04/13/2010.

Claims 1, 3, 5-7, 10-19, 21 are pending and are included in the prosecution.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3, 5-7, 10-19, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of US 6,303,141 ('141), EP 349 430 ('430), Yanagisawa et al. "Angiogenesis-converting enzyme inhibitors" and Bracht "Transdermal therapeutic system: a review".

Applicant Claims

Claim 1 is directed to matrix-controlled transdermal therapeutic system comprising an active-ingredient-impermeable cover layer, self-adhesive matrix layer, or a plurality of matrix layers of which at least the matrix layer exposed while applying the system is self-adhesive, or one or more matrix layers whose surface remote from the cover layer and intended for adhesion at the application site is coated with an adhesive, the matrix layer(s) comprising at least one ACE inhibitor selected from the group consisting of imidapril, fosinopril, moexipril, perindopril, ramipril, spirapril, cilazapril, benazepril and trandolapril, wherein the inhibitor is in the form of a dicarboxylic acid which is derivatised to form a diester, and removable protective layer.

Determination of the Scope and Content of the Prior Art

(MPEP §2141.01)

US '141 teaches transdermal drug delivery device comprising backing layer, matrix containing 10% ACE inhibitor and Eutanol G as permeation enhancer, and protective release liner. The ACE inhibitor is at least one of benzapril, ramipril or trandolapril which are lipophilic prodrugs of the actual active form of the dicarboxylic acid. Esterification of carboxyl group of ACE inhibitor results in more lipophilic substance (abstract; col.1, lines 16-25; col.2, lines 25-30, 37-43; the claims).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Although US '141 teaches active forms of ACE inhibitors as dicarboxylic esterified form of the drug, however, the reference does not specifically teach dicarboxylic acid which is derivatised to form **di**ester as claimed by claim 1. US '141 does not teach the cover over the backing layer that is larger than the backing as claimed by claims 14-17.

The cover sheet and its size do not impart patentability to the claims, absent evidence to the contrary.

EP '430 teaches a transdermal system that has improved flux through the skin achieved by using specific salt forms of the drug (page 2, lines 45-50). The transdermal system has a top layer, a layer containing ACE inhibitor including benzaprilat and

libenzapril, an adhesive layer and protective layer (page 3, lines 40-50). The reference also disclosed on page 3 lines 4-10 the salt forms of the drugs including methane sulphonate and dicarboxylate such as maleate. Claim 3 of the reference teaches lower alkyl dicarboxylate.

Yanagisawa teaches diacid of ACE inhibitor derived from more polar diester was 100 times more patent than one derived from less polar diester (page 423, right column, last paragraph).

Bracht teaches that the use of more lipophilic prodrugs is a strategy to improve the transdermal absorption of molecules. Lipophilic esterification of carboxylic groups can increase the dermal absorption of a drug (page 94, right column, last paragraph).

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide transdermal system for delivery of salts of ACE inhibitors as taught by US '141, and replace the salt of ACE inhibitor by lower alkyl dicarboxylate derivatives of ACE inhibitor taught by EP '430. One would have been motivated to do so because EP '430 teaches that transdermal system that having dicarboxylate derivative of ACE inhibitors showed improved flux through the skin. One would reasonably expect formulating transdermal system for delivery of alkyl dicarboxylate of ACE inhibitors at improved flux rates.

Additionally, one having ordinary skill in the art would have been motivated to use more polar diester to derivatise ACE inhibitor dicarboxylate as taught by Yanagisawa. One would have been motivated to do so because Yanagisawa teaches that more polar diester derivatives of diacid form of ACE inhibitor are 100 times potent than those derived from less polar diester. One would reasonably expected formulating transdermal system for delivery of diester derivative of dicarboxylic acid form of ACE inhibitors that is highly potent to treat hypertension effectively.

Furthermore, one having ordinary skill in the art would have been motivated to use the more lipophilic esters of ACE inhibitors in the transdermal delivery as taught by Bracht because Bracht teaches the use of more lipophilic prodrug obtained by lipophilic esterification of carboxylic groups of drugs is a strategy to improve the transdermal absorption of molecules and can increase the dermal absorption of a drug. One would reasonably expect formulating transdermal system for delivery of diester derivative of dicarboxylic acid form of ACE inhibitors that has improved transdermal absorption.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

5. Applicant's arguments filed 08/10/2010 have been fully considered but they are not persuasive, and moot in view of the new ground of rejection.

Applicants argue that US '141 does not teach diester derivatives of the claimed ACE inhibitors. EP '430 teaches a transdermal system that has improved flux through the skin achieved by using specific salt forms of the drug. The presently claimed invention specifies the active-ingredient to be a diester derivative and not a salt form. Salt forms of ACE inhibitors are not encompassed in the claimed system. EP '430 discloses ACE inhibitors in the form of a dicarboxylic acid salt but not in the form of a diester derivative. Accordingly, one of ordinary skill in the art would recognize that the EP '430 reference would not be suggestive of the claimed diester derivatives.

In response to this argument, it is argued that US '141 teaches transdermal drug delivery device comprising active form of ACE inhibitor, specifically ramipril or trandolapril. US '141 recognized that **esterification of carboxyl group of ACE inhibitor** results in more lipophilic substance ACE inhibitors. The claimed ACE inhibitors contain di-carboxyl group by nature so they are capable to form diester upon esterification process suggested by US '141. US '141 therefore suggested and realized esters of carboxyl group of ACE inhibitors which will inevitably form diester of dicarboxylic acids of ACE inhibitors. EP '430 teaches a transdermal system comprising salt forms of the ACE inhibitors including methane sulphonate and dicarboxylate such as maleate for improved flux through the skin. Therefore, dicarboxylic acid salts and esters of ACE inhibitors were known as taught at the time of the invention and dicarboxylate derivatives of ACE inhibitors can be delivered transdermally. Yanagisawa teaches diester of diacids of ACE inhibitors as being more potent than other derivatives.

One cannot attack the references individually when the rejection is based on combination of the references.

Applicants argue that Yanagisawa nowhere teach or suggest diesters of ACE inhibitors to be potent inhibitors. Yanagisawa merely teach diester derivatives of ACE inhibitors as intermediates for the preparation of the monoethyl ester hydrochlorides 29 a-d, but not as active agents. In fact, Yanagisawa teaches that certain monoester monoacid ACE inhibitor derivatives show a large duration of action.

In response to this argument, applicants' attention is directed to page 423, right column, last paragraph of the reference where the reference clearly teaches **diacid** of ACE inhibitor derived from more polar **diester that** was 100 times more patent than one derived from less polar diester, which is the same concept taught by US '141. Yanagisawa clearly suggests diester to derivatise ACE inhibitor dicarboxylate, and not monoacid as asserted by applicants. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that

the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

Applicants argue that Bracht does not teach or suggest diesters of ACE inhibitors. Bracht is silent about diester derivatives of ACE inhibitor recited in claim 1 and their significantly improved stability in the patch.

In response to this argument it is argued that Bracht is relied upon for the solely teaching of the use of more lipophilic prodrug obtained by lipophilic esterification of carboxylic groups of drugs as a strategy to improve the transdermal absorption of molecules and can increase the dermal absorption of a drug. This teaching would suggested to one having ordinary skill in the art to use **ACE inhibitors having their di-carboxyl group esterified as taught by US '141 and Yanagisawa** that results in more lipophilic substance ACE inhibitors. The combination of the references would results into the present invention.

Applicants argue that the combination of features recited in claim 1 is not taught or suggested by the combination of cited references, since none of the cited references teaches or suggests the claimed diester derivatives of ACE inhibitors as active ingredients of a transdermal therapeutic system, not mention the significantly improved stability of such diester ACE inhibitor derivatives in the patch. There would have been

no reasonable expectation of success in practicing the instantly claimed invention based upon the teachings of the prior art.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide transdermal system for delivery of salts of ACE inhibitors as taught by US '141, and replace the salt of ACE inhibitor by lower alkyl dicarboxylate derivatives of ACE inhibitor taught by EP '430. One would have been motivated to do so because EP '430 teaches that transdermal system that having dicarboxylate derivative of ACE inhibitors showed improved flux through the skin. One would reasonably expect formulating transdermal system for delivery of alkyl dicarboxylate of ACE inhibitors at improved flux rates. Additionally, one having ordinary skill in the art would have been motivated to use more polar diester to derivatise ACE inhibitor dicarboxylate as taught by Yanagisawa. One would have been motivated to do so because Yanagisawa teaches that more polar diester derivatives of diacid form of ACE inhibitor are 100 times potent than those derived from less polar diester. One would reasonably expected

formulating transdermal system for delivery of diester derivative of dicarboxylic acid form of ACE inhibitors that is highly potent to treat hypertension effectively. Furthermore, one having ordinary skill in the art would have been motivated to use the more lipophilic esters of ACE inhibitors in the transdermal delivery as taught by Bracht because Bracht teaches the use of more lipophilic prodrug obtained by lipophilic esterification of carboxylic groups of drugs is a strategy to improve the transdermal absorption of molecules and can increase the dermal absorption of a drug. One would reasonably expect formulating transdermal system for delivery of diester derivative of dicarboxylic acid form of ACE inhibitors that has improved transdermal absorption. Therefore, the examiner believes that motivation to combine the references exists as well as reasonable expectation of success and a prima facie case of obviousness has been established.

It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.*, 425 U.S. 273,282 (1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." In addition, "To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design

community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ". Pp. 11-14. KSR INTERNATIONAL CO. v. TELEFLEXINC. ET AL. (2007).

A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter as a whole as defined by the claims would have been prima facie obvious within the meaning of 35 U.S.C. 103 (a).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

IG

/Isis A Ghali/
Primary Examiner, Art Unit 1611